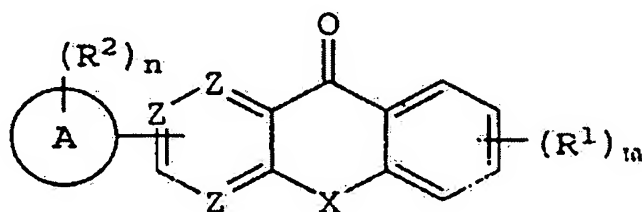


In the Claims

Please replace all prior versions, and listings, of claims in the application with the following list of claims:

Applicant has submitted a complete claim set in which insertions indicated by underlining and strikeouts and/or double bracketing, respectively.

1. (Original) A DNA-PK inhibitor having a formula



or a pharmaceutically acceptable salt thereof,

wherein m is an integer 0 through 3;

n is an integer 0 through 4;

X is O, S(O)₀₋₂, or NR^a;

Z, independently, is CR^b or N;

A is heteroaryl or a four- to seven-membered aliphatic ring containing 0, 1, 2, or 3 heteroatoms independently selected from the group consisting of N, O, and S;

R¹, independently, is selected from the group consisting of halo, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, N(R^d)₂, OR^d, carboxyl, carboxy, nitro, OC₁₋₃alkyleneN(R^d)₂, N(R^d)-C₁₋₃alkyleneN(R^d)₂, OC₁₋₃alkyleneC(=O)OR^d, O(C₁₋₃alkylene)OP(=O)(OR^d)₂, O(C₁₋₃alkylene)OP(=O)(ONa)₂, OP(=O)-(OR^d)₂, OP(=O)(ONa)₂, cyano, aldehyde, carboxamide, thiocarboxamide, acyl, mercapto, sulfonyl, trifluoromethyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl; or

two R¹ groups are taken together with the atoms to which each is attached to form a 5-, 6-, or 7-membered ring, wherein 1 or 2 carbon atoms of R¹ optionally is a heteroatom

selected from the group consisting of O, N, and S, said ring optionally substituted with one or more =O, =S, =NH, OR^c, N(R^d)₂, carboxyl, carboxy, alkyl, aryl, substituted aryl, heteroaryl, or substituted heterocaryl, said heteroatom optionally substituted with a group selected from the group consisting of aryl, substituted aryl, alkyl, substituted alkyl, and acyl;

R², independently, is selected from the group consisting of OR^d, halo, N(R^d)₂, aldehyde, alkyl, substituted alkyl, acyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl,

C₁₋₃alkyleneOR^d, C(=O)N(R^d)₂, N(R^d)₂, (C=O)OR^d, NO₂, NR^dC(=O)R^d, NR^d(SO₂)R^d, OC₁₋₃alkyleneOR^d, OC₁₋₃alkyleneOC₁₋₃alkyleneR^d, OC(=O)R^d, OC₁₋₃alkyleneC(=O)C₁₋₃alkyleneR^d, and (SO₃)R^d;

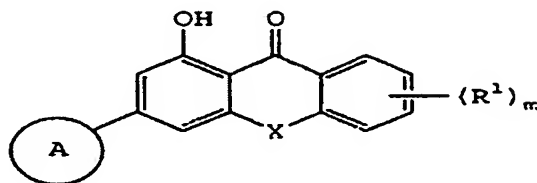
R^a is selected from the group consisting of hydro, C₁₋₄alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, C₁₋₃alkylenearyl, C₁₋₃alkyleneheteroaryl, C₁₋₃alkyleneheterocycloalkyl, C₁₋₄alkylene-N(R^d)₂, C₁₋₄alkyleneOR^d, C₁₋₄alkyleneC(=O)OR^d, C(=O)R^d, C(=O)N(R^d)₂, C(=O)OR^d, C(=O)SR^d, C(=S)N(R^d)₂, SO₂R^d, SO₂N(R^d)₂, C(=O)NR^dC₁₋₄alkyleneOR^d, C(=O)NR^dC₁₋₄alkyleneheterocycloalkyl, C(=O)C₁₋₄alkylenearyl, C(=O)C₁₋₄alkyleneheteroaryl, C₁₋₄alkyleneC(=O)C₁₋₄alkylenearyl, C₁₋₄alkyleneC(=O)C₁₋₄alkyleneheteroaryl, C₁₋₄alkylene-C(=O)heterocycloalkyl, C₁₋₄alkyleneNR^dC(=O)R^d, C₁₋₄alkyleneOC₁₋₄alkyleneOR^d, C₁₋₄alkyleneOC₁₋₄alkyleneC(=O)OR^d, and C₁₋₄alkyleneC(=O)N(R^d)₂;

R^b, independently, is selected from the group consisting of hydro, alkyl, halo, aldehyde, OR^d, O(C₁₋₃alkylene)OP(=O)(OR^d)₂, O(C₁₋₃alkylene)OP(=O)(ONa)₂, OP(=O)(OR^d)₂, OP(=O)(ONa)₂, nitro, N(R^d)₂, carboxyl, carboxy, sulfonamido, sulfamyl, and sulfo or a halide derivative thereof; and

R^d, independently, is selected from the group consisting of hydro, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, C₁₋₃alkylenearyl, substituted aryl, heteroaryl, and substituted heteroaryl.

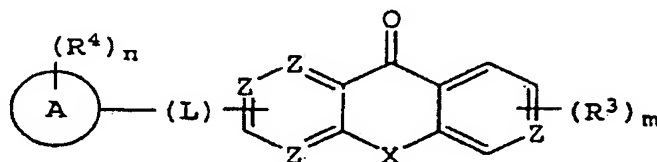
2-8. (Canceled)

9. (Original) The inhibitor of claim 1 having a structure



10. (Canceled)

11. (Original) A DNA-PK inhibitor having a formula:



or a pharmaceutically acceptable salt thereof,

wherein m is an integer 0 through 3;

n is an integer 0 through 4;

X is O or NR^a ;

Z , independently, is CR^b or N;

L is selected from the group consisting of alkylene, substituted alkylene, carbonyl, carbamoyl, $-\text{NR}^d$, $-\text{N}(\text{R}^d)_2$, $-\text{O}(\text{SO}_2)\text{R}^d$, $-\text{SO}_2\text{R}^d$, oxy ($-\text{O}-$), thio ($-\text{S}-$), thionyl ($-\text{SO}-$), and sulfonyl;

A is absent, or A is heteroaryl or a four-to seven-membered aliphatic ring containing 0, 1, 2, or 3 heteroatoms independently selected from the group consisting of N, O, and S;

R^1 , independently, is selected from the group consisting of halo, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, $\text{N}(\text{R}^d)_2$, OR^d , carboxyl, carboxy, nitro, $\text{OC}_{1-3}\text{alkyleneN}(\text{R}^d)_2$, $\text{N}(\text{R}^d)_{1-3}\text{alkyleneN}(\text{R}^d)_2$, OC_1 .

$3\text{alkyleneC(=O)OR}^d$, $\text{O(C}_{1-3}\text{alkylene)OP(=O)(OR}^d)_2$, $\text{O(C}_{1-3}\text{alkylene)OP(=O)(ONa)}_2$, $\text{OP(=O)(OR}^d)_2$, OP(=O)(ONa)_2 , cyano, aldehyde, carboxamide, thiocarboxamide, acyl, mercapto, sulfonyl, trifluoromethyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl; or

two R^1 groups are taken together with the atoms to which each is attached to form a 5-, 6-, or 7-membered ring, wherein 1 or 2 carbon atoms of R^1 optionally is a heteroatom selected from the group consisting of O, N, and S, said ring optionally substituted with one or more of $=\text{O}$, $=\text{S}$, $=\text{NH}$, OR^c , $\text{N(R}^d)_2$, carboxyl, carboxy, alkyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl, and said heteroaryl optionally substituted with a substituent selected from the group consisting of aryl, substituted aryl, alkyl, substituted alkyl, and acyl;

R^2 , independently, is selected from the group consisting of OR^d , halo, $\text{N(R}^d)_2$, aldehyde, alkyl, substituted alkyl, acyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, $\text{C}_{1-3}\text{alkyleneOR}^d$, $\text{C(=O)N(R}^d)_2$, $\text{N(R}^d)_2$, C(=O)OR^d , NO_2 , $\text{NR}^d\text{C(=O)R}^d$, $\text{NR}^d(\text{SO}_2)\text{R}^d$, $\text{OC}_{1-3}\text{alkyleneOR}^d$, $\text{OC}_{1-3}\text{alkyleneOC}_{1-3}\text{alkyleneR}^d$, OC(=O)R^d , $\text{OC}_{1-3}\text{alkyleneC(=O)C}_{1-3}\text{alkyleneR}^d$, and $(\text{SO}_3)\text{R}^d$;

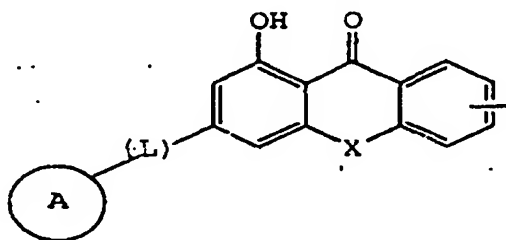
R^a is selected from the group consisting of hydro, $\text{C}_{1-4}\text{alkyl}$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, $\text{C}_{1-3}\text{alkylenearyl}$, $\text{C}_{1-3}\text{alkyleneheteroaryl}$, $\text{C}_{1-3}\text{alkyleneheterocycloalkyl}$, $\text{C}_{1-4}\text{alkylene-N(R}^d)_2$, $\text{C}_{1-4}\text{alkyleneOR}^d$, $\text{C}_{1-4}\text{alkyleneC(=O)OR}^d$, C(=O)R^d , $\text{C(=O)N(R}^d)_2$, C(=O)OR^d , C(=O)SR^d , $\text{C(=S)N(R}^d)_2$, SO_2R^d , $\text{SO}_2\text{N(R}^d)_2$, $\text{C(=O)NR}^d\text{C}_{1-4}\text{alkyleneOR}^d$, $\text{C(=O)NR}^d\text{C}_{1-4}\text{alkyleneheterocycloalkyl}$, $\text{C(=O)C}_{1-4}\text{alkylenearyl}$, $\text{C(=O)C}_{1-4}\text{alkyleneheteroaryl}$, $\text{C}_{1-4}\text{alkyleneC(=O)C}_{1-4}\text{alkylenearyl}$, $\text{C}_{1-4}\text{alkyleneC(=O)C}_{1-4}\text{alkyleneheteroaryl}$, $\text{C}_{1-4}\text{alkyleneC(=O)heterocycloalkyl}$, $\text{C}_{1-4}\text{alkyleneNR}^d\text{C(=O)R}^d$, $\text{C}_{1-4}\text{alkyleneOC}_{1-4}\text{alkyleneOR}^d$, $\text{C}_{1-4}\text{alkyleneOC}_{1-4}\text{alkylene-C(=O)OR}^d$, and $\text{C}_{1-4}\text{alkyleneC(=O)N(R}^d)_2$;

R^b , independently, is selected from the group consisting of hydro, alkyl, halo, aldehyde, OR^d , $\text{O(C}_{1-3}\text{alkylene)OP(=O)(OR}^d)_2$, $\text{O(C}_{1-3}\text{alkylene)OP(=O)(ONa)}_2$, $\text{OP(=O)(OR}^d)_2$, OP(=O)(ONa)_2 , nitro, $\text{N(R}^d)_2$, carboxyl, carboxy, sulfonamido, sulfamyl, and sulfo or a halide derivative thereof; and

R^d , independently, is selected from the group consisting of hydro, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, C_{1-3} alkylenearyl, substituted aryl, heteroaryl, and substituted heteroaryl.

12-19. (Canceled)

20. (Original) The inhibitor-of claim 11 having a structure



and prodrugs thereof.

21. (Canceled)

22. (Original) A DNA-PK inhibitor selected from the group consisting of:
trifluoromethanesulfonic acid 1-hydroxy-9-oxo-9H-xanthen-3-yl ester;
1-hydroxy-3-morpholin-4-yl-xanthen-9-one;
1-hydroxy-6-methoxy-3-trifluoromethanesulfonylxanthen-9-one ester;
1-hydroxy-6-methoxy-3-morpholin-4-yl-xanthen-9-one;
6-fluoro-1-hydroxy-3-morpholin-4-yl-xanthen-o-one;
1-hydroxy-6-(4-methylpiperazin-1-yl)-3-morpholin-4-yl-xanthen-9-one;
1-(8-hydroxy-6-morpholin-4-yl-9-oxo-9H-xanthen-3-yl)-piperidine-4-carboxylic acid amide; trifluoromethanesulfonic acid 1-hydroxy-9-oxo-9,10-dihydro-acridin-3-yl ester; and 1-hydroxy-3-morpholin-4-yl-10H-acridi-9-one.

23. (Currently amended) A pharmaceutical composition comprising (a) DNA-PK inhibitor of claim 1 [[or claim 11,]] and (b) a pharmaceutically acceptable carrier or diluent.

24. (Currently amended) A pharmaceutical composition comprising (a) a DNA-PK inhibitor of claim 1 [[or 11,]] and (b) an antineoplastic agent.

25-29. (Canceled)

30. (Currently amended) A method of inhibiting DNA-PK activity comprising the step of contacting a DNA-PK with a DNA-PK inhibitor of claim 1 [[or 11]].

31. (Currently amended) A method of sensitizing a cell type to an agent that induces DNA lesions comprising the step of contacting the cell type with a compound of claim 1 [[or 11]].

32. (Canceled)

33. (Currently amended) A method of potentiating a therapeutic regimen for treatment of a cancer comprising the step of administering to an individual in need thereof an effective amount of a DNA-PK inhibitor of claim 1 [[or 11]].

34. (Canceled)

35. (Currently amended) A method of characterizing the potency of a test compound as an inhibitor of a DNA-PK polypeptide, said method comprising the steps of:

a) measuring an activity of a DNA-PK polypeptide in the presence of a test compound;

b) comparing the activity of the DNA-PK polypeptide in the presence of the test compound to the activity of the DNA-PK polypeptide in the presence of an equivalent amount of a reference compound of claim 1 [[or 11]], wherein a lower activity of the DNA-PK polypeptide in the presence of the test compound than in the presence of the reference compound indicates that the test compound is a more potent inhibitor than the reference compound, and a higher activity of the DNA-PK polypeptide in the presence of the test

compound than in the presence of the reference compound indicates that the test compound is a less potent inhibitor than the reference compound.

36. (Currently amended) A method of characterizing the potency of a test compound as an inhibitor of a DNA-PK polypeptide, said method comprising the steps of:

a) determining an amount of a control compound of claim 1 [[or 11]] that inhibits an activity of a DNA-PK polypeptide by a reference percentage of inhibition, thereby defining a reference inhibitory amount for the control compound;

b) determining an amount of a test compound that inhibits an activity of a DNA-PK polypeptide by a reference percentage of inhibition, thereby defining a reference inhibitory amount for the test compound;

c) comparing the reference inhibitory amount for the test compound to a reference inhibitory amount determined according to a step (a) for the control compound, wherein a lower reference inhibitory amount for the test compound than for the control compound indicates that the test compound is a more potent inhibitor than the control compound, and a higher reference inhibitory amount for the test compound than for the control compound indicates that the test compound is a less potent inhibitor than the control compound.

37-39. (Canceled)

40. (Currently amended) An article of manufacture comprising:

a) an anticancer compound that induces double-strand DNA breakage in cells;
and

b) a package insert describing a coordinated administration to a patient of said anticancer compound and a DNA-PK inhibitor compound of claim 1 [[or 11]].

41-45. (Canceled)

46. (New) A pharmaceutical composition comprising (a) DNA-PK inhibitor of claim 11 and (b) a pharmaceutically acceptable carrier or diluent.
47. (New) A pharmaceutical composition comprising (a) a DNA-PK inhibitor of claim 11 and (b) an antineoplastic agent.
48. (New) A method of inhibiting DNA-PK activity comprising the step of contacting a DNA-PK with a DNA-PK inhibitor of claim 11.
49. (New) A method of sensitizing a cell type to an agent that induces DNA lesions comprising the step of contacting the cell type with a compound of claim 11.
50. (New) A method of potentiating a therapeutic regimen for treatment of a cancer comprising the step of administering to an individual in need thereof an effective amount of a DNA-PK inhibitor of claim 11.
51. (New) A method of characterizing the potency of a test compound as an inhibitor of a DNA-PK polypeptide, said method comprising the steps of:
- a) measuring an activity of a DNA-PK polypeptide in the presence of a test compound;
 - b) comparing the activity of the DNA-PK polypeptide in the presence of the test compound to the activity of the DNA-PK polypeptide in the presence of an equivalent amount of a reference compound of claim 11, wherein a lower activity of the DNA-PK polypeptide in the presence of the test compound than in the presence of the reference compound indicates that the test compound is a more potent inhibitor than the reference compound, and a higher activity of the DNA-PK polypeptide in the presence of the test compound than in the presence of the reference compound indicates that the test compound is a less potent inhibitor than the reference compound.

52. (New) A method of characterizing the potency of a test compound as an inhibitor of a DNA-PK polypeptide, said method comprising the steps of:

a) determining an amount of a control compound of claim 11 that inhibits an activity of a DNA-PK polypeptide by a reference percentage of inhibition, thereby defining a reference inhibitory amount for the control compound;

b) determining an amount of a test compound that inhibits an activity of a DNA-PK polypeptide by a reference percentage of inhibition, thereby defining a reference inhibitory amount for the test compound;

c) comparing the reference inhibitory amount for the test compound to a reference inhibitory amount determined according to a step (a) for the control compound, wherein a lower reference inhibitory amount for the test compound than for the control compound indicates that the test compound is a more potent inhibitor than the control compound, and a higher reference inhibitory amount for the test compound than for the control compound indicates that the test compound is a less potent inhibitor than the control compound.

53. (New) An article of manufacture comprising:

a) an anticancer compound that induces double-strand DNA breakage in cells;
and

b) a package insert describing a coordinated administration to a patient of said anticancer compound and a DNA-PK inhibitor compound of claim 11.